REMARKS

Continued prosecution and consideration of the claimed subject matter in the accompanying patent application is respectfully requested.

Claims 26, 41, 46, 54 and 58 have been amended. Claims 26, 31-32, 34, 36-41, 46, 52-56, 58 and 60-61 are in the case and are before the Examiner. Claims 42-45 and 47-51 were previously withdrawn.

I. The Amendments

Independent claims 26, 41, 46, 54 and 58 have been amended to more clearly define the invention and to speed prosecution. More specifically, those claims have been amended to recite that the antigen part of the fusion protein "consists essentially of an immunogenic extracellular part of an M2 membrane protein of a human influenza A virus as defined by SEQ ID NOs: 1, 2 or 3, or a functional fragment thereof that elicits a statistically significant higher immunoprotection when administered in an immunoprotective dose to test members of a species than is found in control members of the same species not receiving the functional fragment," and thereby still more clearly recites that only an external part of the M2 protein is used as antigen. This amendment is supported at least by the disclosures of paragraphs [0058] and [0059] of the published application No. 20060246092.

These amendments add no new matter.

II. The Action

A. Withdrawal of Rejections

The withdrawal of the previous rejections based on Pumpens in view of Slepushkin and further in view of Sunstrom or Hongo are noted with appreciation.

B. Claim Interpretation

Relying on MPEP Chapter 2111.03, the Action has characterized the previous Reply's claim recitation that includes the transitional phrase "consisting essentially of" as if it were "comprising"; i.e., as open and thereby including the entire M2 sequence. This basis for interpretation cannot be agreed with and is respectfully traversed.

The asserted basis for the above interpretation is that "the Office interprets the antigen to *comprise* the immunogenic extracellular part of M2, is that the specification fails to define the metes and bounds of the antigen that *consists essentially of* an immunogenic extracellular part of an M2 membrane protein." (Emphasis in the original.) On the contrary, it is submitted that the specification teaches those metes and bounds, and provides a clear indication of what the basic and novel characteristics actually are; i.e., the 24-mer extracellular portion of a functional fragment thereof.

Thus, the Examiner's attention is invited to paragraph [0056] of the published application that states in part "[i]mmunization with complete M2 protein in humans as described [by Slepushkin et al.] is not realistic because it relies on incomplete Freund's adjuvant which cannot be used in humans, and is counter-indicated in higher animals." It must also be remembered that M2 is a membrane protein whose residues down stream from the external portion are hydrophobic which a skilled

worker in the year 2000 would know could cause difficulty as part of a vaccine preparation.

Two paragraphs later, in paragraph [0058], the specification continues with the following:

> it has now been found that it is possible to prepare such a novel antigen that does not exist in nature. For this the extracellular part of a conserved influenza membrane protein or a functional fragment thereof is fused to a presenting carrier,. . . The conserved influenza membrane protein is for example the well conserved, extracellular part of the M2 protein . . ."

The next paragraph defines the meaning of a `functional fragment` of that extracellular portion. The following paragraph provides an illustrative example using a 23-residue portion of the 24-residue extra cellular domain. Still further, Table 1 that follows paragraph [0053] illustrates several of the conserved sequences of that extracellular portion. Importantly, no longer sequence is shown or discussed as useful in the invention.

Additionally, the claims have been amended top recite that the antigen portion has the sequence of one of three numbered sequences, or a functional fragment of such a sequence. Those are the sequences of the conserved extracellular portions of M2 that are illustrated in Table 1.

It is therefore submitted that the specification clearly teaches the metes and bounds of the "consisting essentially of" language as it is applied to the extracellular portion of the M2 protein as antigen, and provides a clear indication of what are the basic and novel characteristics of that sequence. It is therefore requested that the interpretation given to the "consisting essentially of" phrase be given its usual meaning of a specified sequence and those

that do not materially affect the basic and novel characteristic(s) of the claimed invention.

C. Rejections Under 35 USC §103

1. First Rejection

Claims 26, 31, 32, 36, 38, 41, 46, 53-56 and 58-61 were again rejected as allegedly obvious from the combined teachings of Pumpens et al, *Intervirology*, 1995 **38**:63-74 (Pumpens) and Slepushkin et al., *Vaccine*, 1995 **13(15)**:1399-1402 (Slepushkin). Briefly, Pumpens teaches that HBcAg or HBc particles are good epitope carriers and can accommodate epitopic sequences at the N-, or C-terminus as well as within the sequence. Slepushkin is said to teach that the full length M2 protein is highly conserved and could function as a subunit vaccine to protect mice upon expression in a baculovirus membrane preparation to protect mice from challenge, but could not protect mice from challenge when expressed as part of a vaccinia recombinant.

The present Action asserts that the claims are not limited to an extracellular portion of the M2 protein. As noted above, it is submitted that the claims were and are so limited, or to a still shorter portion thereof. The Action continues by asserting that even if the claims were so limited, they would still be obvious because the extracellular portion is part of the whole and

> is more exposed initially to the immune system than the intracellular part of the protein. . . .the immune system must first recognize the virus as being non-self, and then respond appropriately. The proteins that are exposed on the virion include the extracellular portion of the M2 protein. . . .[The Office's position is] that the response to the extracellular portion of the M2 protein would be valuable because it is readily exposed to the immune system upon infection. (Action, page 6.)

It is respectfully submitted that the above bases for rejection include erroneous misconceptions whose disclosure will convince the Examiner of the non-obviousness of the presently claimed invention.

It is first noted that during an influenza epidemic, a fraction of infected people respond by making anti-M2e-antibodies, and usually this response is a transient [Black et al. (E29) and Gerhard et al. (F5) that are believed to be of record]. If under conditions of natural infection, when synthesis of natural, full-length M2-protein occurs, a fraction of the population has anti-M2-antibodies in their circulation, one would expect that these individuals would be protected when the next epidemic with a slightly different HA- but same M2e-sequence comes along. But such a cross-protection has never been observed.

The results described in the relied-on Slepushkin paper are due to a totally different part of the immune system from that impacted by a contemplated fusion protein. Thus, that paper deals with cellular immunity as opposed to humoral (antibody-based) immunity here. Indeed, Slepushkin failed to transfer protection by serum (where antibodies reside) (p. 1402). In contrast, the inventors here document that the protection against a lethal influenza infection is transferable by serum ("passive immunization"), and therefore is due to antibodies. Passive transfer of protection was also shown by Treanor (E 28) who reported that a monoclonal antibody, MAb 14C2, can be used for passive immunization and does protect against a challenge.

In discussing the failure of transferring protection by serum, Slepushkin come to the conclusion that cell-based immune mechanisms are involved. He also mentions preliminary

results confirming the induction of M2-protein directed cytotoxic T-cells (CTL). An immune T-cell response is triggered by a completely different pathway from that claimed here. In that case, to stimulate a CTL response, a protein containing one or more naturally occurring cytotoxic T-cell epitope(s) must be processed intracellularly by a presenting cell so that the trimmed T-cell epitope-containing peptide is presented in the proper context (the so-called complex I). This pathway is not helped by linking a B cell antigen to a presenting carrier, as is used by the present inventors.

Slepushkin mention that anti-M2 antibodies could play a role in the antiviral response. Because he offers no experimental evidence for this claim, the worker of ordinary skill at the time would not deem it to be a proper suggestion. Evidence for an accessory role of antibodies in T-cell mediated protection could have been demonstrated by passively transferring T-cells together with or without serum from M2-protein treated animals.

In the absence of experimental evidence, speculation is wide open. Even if antibodies play an accessory role in Slepushkin's system (involving total M2-protein), it could likely be antibodies directed to the C-terminal peptide, which he has identified as the most immunogenic region. That is particularly the case because the M2e portion that is exterior to the virion does not provide protection against subsequent infection.

Thus, it is submitted again that the Slepushkin disclosures are not properly combinable by a forward-looking skilled worker with those of Pumpens. Rather, the combination only occurs in hindsight after having read the present disclosure. That forward looking worker would hardly expect a

sequence such as that of M2e that is not protective in its natural environment to provide protection when bonded to a carrier as a fusion protein. The fact that protection is obtained with such a construct is actually quite surprising. It is again submitted that this basis for rejection should be withdrawn.

B. Second Rejection

Claim 37, "wherein the fusion product [of the immunogenic composition of claim 26] is anchored in the membrane of an acceptor cell expressing the fusion product" has been again been rejected over the combined teachings of Pumpens and Slepushkin as above further in view of Highfield et al., AU-B-49273/90. The Highfield disclosure is used to support the assertion that a skilled worker could express "a fusion construct from any acceptable cell line." The Action asserts that the previous arguments against this rejection were discussed previously. This basis for rejection cannot be agreed with for several reasons and is respectfully traversed.

First, as noted above, the combination of teachings of Pumpens and Slepushkin does not lead one of ordinary skill to the subject matter of claim 26 and therefore the addition of the Highfield disclosures that add nothing regarding the deficiencies of those teachings cannot make dependent claim 37 obvious. Thus, again, this basis for rejection should be withdrawn.

Second, even if the combination of the Pumpens and Slepushkin teachings were to lead a skilled worker to the subject matter of claim 26, and even if Highfield teaches that a skilled worker could express "a fusion construct from any acceptable cell line", neither of which is believed to be the

case, it is submitted that a teaching of expression in "any acceptable cell line" is quite different from expression that leads to "the fusion product [of claim 26 being] anchored in the membrane of an acceptor cell expressing the fusion product" as is claimed.

It is again submitted that the prior and present amendments clarify that only an extracellular portion of the M2 protein is used. That being the case, and based on the logic expressed in the Action, if the whole protein were membrane-bound and the portion used here sticks out, away from the membrane into the fluids, one would expect the claimed fusion protein to not be membrane-bound, but to be secreted as its antigen portion is normally found in fluid, not a membrane. Contrary to that expectation, the fusion protein is membrane-bound and as such, this basis for rejection should be withdrawn.

c. Third Rejection

Claims 34 and 39 were again rejected as allegedly obvious from the combined teachings of Pumpens and Slepushkin as in the first rejection and Highfield in the second rejection further in view of van de Guchte et al., *Appl. Environm. Microbiol.* 1989 **55(1):**224-228 (van de Guchte). The van de Guchte disclosure teaches lactococcal expression vectors that can express a wide range of heterologous genes. This basis for rejection cannot be agreed with and is respectfully traversed.

The arguments provided above in response to the above Second Rejection are repeated here by reference. As such, it is submitted that there is no expectation of success in regard to the recited and above quoted subject matter regarding expression of the immunogenic materials in or on the Lactococci cell walls.

It is thus submitted that this basis for rejection should also be withdrawn.

It is further submitted that the added disclosures of van de Guchte et al. are not seen that would lead one to believe that an expressed fusion protein would find its way to and remain in or on the surface of the expressing cell. As a consequence, it is again submitted that this basis for rejection should be withdrawn.

D. Fourth Rejection

Claims 40 and 52 that depend from claim 26 have been rejected over the combined teachings of Pumpens and Slepushkin as discussed above, further in view of Kedar et al. US Patent No. 5,919,480 (Kedar). The Kedar patent is said to disclose the influenza hemagglutinin and neuraminidase proteins in combination with a cytokine as a vaccine. The Action asserts that it would be obvious to add known vaccine antigens and an immunostimulating cytokine in influenza immunogenic composition of claim 26. This basis for rejection cannot be agreed with and is respectfully traversed.

The previously-made arguments concerning the inapplicability of the combination of the Pumpens and Slepushkin teachings to suggestion of the immunogenic composition of claim 26 are repeated here. It is apparent that with no mention being made of a carrier such as HBc, a fusion protein or the M2 protein, the Kedar patent has no disclosures that could overcome the deficits already noted in the Pumpens and Slepushkin teachings regarding the claimed subject matter. Inasmuch as the subject matter claimed in claims 40 and 52 is dependent upon claim 26, and because that independent claim is not obvious from the basic Pumpens and Slepushkin teachings, the dependent claim

cannot be obvious from a teaching that does not augment the first two disclosures. This basis for rejection should therefore be withdrawn.

III. Summary

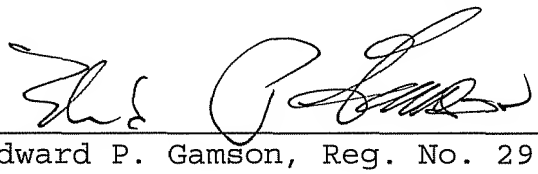
Independent claims 26, 41, 46, 54 and 58 have been amended. Each basis for rejection or objection has been overcome or otherwise made moot.

It is therefore believed that this application is in condition for allowance of all of the pending claims. An early notice to that effect is earnestly solicited.

No further fee or petition is believed to be necessary. However, should any further fee be needed, please charge our Deposit Account No. 23-0920, and deem this paper to be the required petition.

The Examiner is requested to phone the undersigned should any questions arise that can be dealt with over the phone to expedite this prosecution.

Respectfully submitted,

By 

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